REMARKS

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 are pending. Claims 15, 21, 42, 48, and 60-62 been amended. After entry of the present amendment, claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 will be pending in the application.

Support for the amendments to claims 15, 21, 42, and 48 can be found throughout the specification as filed, for example, at page 19, lines 4-14 and at page 27, line 25.

No new matter has been added. Applicants reserve the right to pursue the claims, as originally filed, or similar claims in this or one or more subsequent patent applications.

Withdrawal of Previous Rejections

Applicants thank the Examiner for the withdrawal of the previous rejection of claims 15-17, 21, 22, 24, 31, 42, 43, 48 and 57-59 under 35 U.S.C. § 102(b) or in the alternative 35 U.S.C. § 103(a) in view of Le *et al.*

Rejection Under 35 U.S.C. § 112, First Paragraph - Written Description

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 60-62 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to meet the written description requirement. The Examiner acknowledges that "Applicant is in possession of the method of claim 15 if it is limited to 'a low dose of 0.1-0.21 mg/kg at a frequency of once per week' or the methods of claims 21 and 42 if they are limited to 'a low dose of 0.06-0.21 mg/kg at a frequency of once per week'" but also states that Applicants are "not in possession of the breadth of currently claimed methods of treatment". Applicants respectfully traverse the rejection.

While Applicants respectfully disagree with the Examiner's maintenance of the rejection, the claims have been amended *solely in the interest of expediting prosecution and in no way acquiescing to the Examiner's rejection.* Specifically, claim 15 has been amended to specify a weekly low dose of 0.10-0.21 mg/kg. Claims 21, 42, and 48 have been amended to specify a weekly low dose of 0.06-0.21 mg/kg. Reconsideration and withdrawal of the rejection of claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48, and 60-62 under 35 U.S.C. § 112, first paragraph is respectfully requested.

Rejection of Claims 17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 Under 35 U.S.C. § 112, 2nd Paragraph

The Examiner has rejected claims 17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 under 35 U.S.C. § 112, 2nd paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Examiner states that:

> The instant claims recite "at a low dose of about 0.06-0.21 mg/kg" (see claims 15,21,42,48) and similar like claim 62 "wherein the low dose is about 0.09-0.11 mg/kg." The metes and bounds of this limitation would not be clear to the skilled artisan because the instant specification does not provide any explicit guidance or direction as to what is meant by the relative term "about" as it is applied to the mg/kg antibody being administered in the instant claims. (5th paragraph, page 10 of Office Action)

While Applicants respectfully disagree with the Examiner's rejection, the claims have been amended *solely in the interest of expediting prosecution and in no way acquiescing to the Examiner's rejection*. Specifically, the term "about" has been deleted from those claims in which the term appeared, *i.e.*, claims 15, 21, 42, 48 and 60-62.

Reconsideration and withdrawal of the rejection of claims 17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 under 35 U.S.C. § 112, 2nd paragraph is respectfully requested.

Rejection of Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 Under 35 U.S.C. § 103(a)

Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48 remain rejected, and claims 60-62 are newly rejected, under 35 U.S.C. § 103(a) as allegedly being obvious over Schattenkirchner (Presented at: The Annual Meeting of the European League Against Rheumatism (EULAR, Prague, Czech Republic, June 2001)), in view of den Broeder et al. (Rheumatology (Oxford) 41(6): 638-642, June, 2002, of record, or "den Broeder" hereinafter), Salfeld et al. (U.S. Pat. No. 6,258,562, of record, or "Salfeld" hereinafter), Kim et al. (Arthritis & Rheumatism 43(3): 473-484, March, 2000, or "Kim" hereinafter), and Stephens et al. (Antibody Therapeutics (1997), pp 317-340, eds. Harris et al., CRC: Boca Raton, FL, or "Stephens" hereinafter), "essentially for the reasons of record as put forth in the Office Action mailed August 5, 2010." Applicants respectfully traverse the rejection.

In making the obviousness rejection, the Examiner argues that Schattenkirchner (the primary reference cited) teaches a method of treating arthritis using 0.5 mg/kg D2E7 on a weekly basis, but fails to teach weekly administration of less than 0.5 mg/kg per week of D2E7. However, the Examiner argues that den Broeder, Salfeld, Kim, or Stephens provide motivation and reasonable expectation of success to lower the dosage level down by five folds to arrive at the presently claimed invention.

"To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations." (See MPEP § 2143; emphasis added).

Independent claim 15 is directed to a method for treating arthritis comprising administering by injection to a subject an isolated fully human anti-TNFα antibody, or an antigen-binding portion thereof, at a weekly low dose of 0.10-0.21 mg/kg. Independent claim 21 is directed to a low dose method for alleviating at least one symptom associated with arthritis comprising administering by injection to a subject an isolated fully human anti-TNFα antibody, or an antigen-binding portion thereof, at a weekly low dose of 0.06-0.21 mg/kg. Independent claim 42 is directed to a low dose method for treating rheumatoid arthritis comprising administering by injection to a subject at a weekly low dose of 0.06-0.21 mg/kg of a fully human TNFα antibody, or antigen-binding portion thereof. Independent claim 48 is directed to a low dose method of improving symptoms in the joints of a subject having arthritis comprising administering by injection to the subject a weekly low dose of 0.06-0.21 mg/kg of a fully human anti-TNFα antibody, or antigen-binding portion thereof.

Applicants submit that none of the cited secondary references make up for the deficiency of Schattenkirchner and do not teach or suggest using dose amounts less than 0.5 mg/kg.

den Broeder Reference

In the Office Action mailed August 5, 2010, the Examiner states that "it would have been obvious to one of ordinary skill in the art to titrate the dose of Schttenkirchner below 0.5 mg/kg on weekly basis" (see page 12, 3rd paragraph). For support, the Examiner alleges that:

> "[o]ne of ordinary skill in the art would have had a reasonable expectation of success in doing so based on the teachings of den Broeder ("There is marked

variation in the individual dose of anti-TNFa needed to maintain clinical efficacy" and "As no smaller dose steps than 0.25 mg/kg were included, one could speculate that even further reduction is possible for individual patients. This is supported by the remarkably long duration of response seen in some patients after only one administration of anti-TNFa, document for. ..D2E7 (up to 14 weeks EULAR response)... ") and further based on the teachings of Salfeld that an effective dose of the D2E7 anti-TNFa antibody is 0.1 - 20 mg/kg." (page 12, 4th paragraph).

Applicants respectfully disagree.

The den Broeder reference discloses a study in which 21 patients whose RA was being stably treated at 3.0 mg/kg had their doses reduced over a 48 week period. Some of the patients were being treated with 3.0 mg/kg every two weeks, some every four weeks. Regardless of the frequency of dosing, all patients had their doses reduced in a step-wise fashion, until their disease symptoms flared. The dosages described in den Broeder were 1.0 mg/kg, 0.5 mg/kg and 0.25 mg/kg.

Notably, the authors of den Broeder state the following: "Six out of the 21 patients were placed back on the original dose of 3.0 mg/kg (please check) after flaring on 1.0 mg/kg whereas nine, three and three patients respectively reached a dose of 1.0, 0.5 and 0.25 mg/kg." (page 639, 2nd column, last paragraph to page 640, 1st column, 1st paragraph); "Eighteen patients flared during the study" (page 640, 2nd column, 2nd paragraph); and "Three patients did not experience a flare even on the lowest dose of 0.25 mg/kg anti-TNFα." (page 640, 2nd column, 2nd paragraph. In addition, Figure 1 (page 640) of den Broeder shows the dosage history for one patient in the study who flared when the dosage reached 0.5 mg/kg; as noted in the figure legend, "[a]fter the dose of anti-TNF-α had been increased to 1.0 mg/kg, the DAS28 returned to the previously low level."

Given the above exemplary teachings of den Broeder, one of ordinary skill in the art would have understood that the researchers were reducing the dosages until a flare-up occurred, at which point the dosage was returned to the next highest step in order to reduce the patient's DAS28 score to the previous lower levels. Furthermore, one of ordinary skill in the art would have understood that eighteen of the 21 patients experienced a disease flare at a dosage of 0.25 mg/kg a week or greater, and needed to be given a higher dosage in order to effectively treat RA symptoms as demonstrated by DAS28 scores. In particular, one of ordinary skill in the art would have understood that a dosage of 1.0 mg/kg was insufficient for 29% of the patients studied, a dosage of 0.5 mg/kg was insufficient for 71% of the patients studied and a dosage of 0.25 mg/kg was insufficient for 86% of the patients studied.

With regard to the quotations of the den Broeder reference made by the Examiner regarding "further reductions" (*i.e.* "As no smaller dose steps than 0.25 mg/kg were included, one could speculate that even further reduction is possible for individual patients"), Applicants note that the Examiner appears to maintain the position that the den Broeder actually teaches or suggests a dosage of less than 0.25 mg/kg, as explicitly stated in previous Office Actions. For example, in the Office Action mailed August 8, 2007, the Examiner states that

> [w]hile den Broeder teaches their trial was not designed to include anti-TNFa antibody dose steps smaller than 0.25 mg/kg, ***den Broeder further teaches that the anti-TNFa antibody dosage could be even further reduced*** in light of the absence of any disease flare-ups in the patients treated with 0.25 mg/kg D2E7 every 2-4 weeks. (page 12, 2nd paragraph, emphasis added).

Applicants respectfully submit that the Examiner has mischaracterized the reference and that the "further reductions" contemplated by the authors are reductions in "the median weekly amount of anti-TNF-α" given to study patients in terms of mg/week, not in the dosage in mg/kg. As noted by the authors in the paragraph from which the Examiner took the quotation:

> [i]n spite of the relatively small number of patients, we found marked variation in the required dose of anti-TNF-α. Required doses ranged from 4.1 to 130 mg/week. Using the titration regimen described above, the median weekly amount of anti-TNF-α given to these patients could be lowered by 67%, ***from 97.5 to 32.5 mg/week***. As no smaller dose steps than 0.25 mg /kg were included, one could speculate that ***even further reduction*** is possible for individual patients. (page 641, 2nd paragraph, emphasis added)

Thus the authors are clearly referring to an "even further reduction" in the median amount of drug used per week for the patients of the study, in terms of mg/week, and not to a reduction in the mg/kg dosage.

The Examiner has relied on the den Broeder reference for providing predictability and a reasonable expectation of success to one of ordinary skill in the art "to titrate the dose of Schattenkirchner below 0.5 mg/kg on weekly basis." However, given that there is no teaching or suggestion to attempt a dosage lower than 0.25 mg/kg, and given that nearly 90% of the patients failed to be treated by dosages less than 0.5 mg/kg in the study of den Broeder, Applicants respectfully submit that one of ordinary skill in the art would have no motivation to reduce the dosage of Schattenkirchner based on the teachings of den Broeder and achieve the methods of the present claims, and no reasonable expectation of success in doing so.

Salfeld Reference

The Examiner has maintained that the Salfeld reference provides a reasonable expectation of success to one of ordinary skill in the art for lowering the dosage of Schattenkirchner below 0.5 mg/kg weekly, because "Salfeld teaches a method of treating rheumatoid arthritis by administering a human anti-TNFα antibody, such as D2E7", "further teaches that an effective dose of anti-TNFα antibody is 0.1-20 mg/kg, and that the anti-TNFα antibody dosage concentration and frequency is a results-effective variable that should be 'adjusted over time according to the individual need and the professional judgment of the person administering or supervising the administration of the compositions'". Notably, the Examiner has previously acknowledged (and still does not dispute) that "Salfeld recites … the range of 0.1-20 mg/kg, and that Salfeld recites this dosage range without concurrently reciting a frequency of administration."

Applicants also reiterate (which the Examiner does not dispute) that, while Salfeld describes and enables all of the embodiments described and claimed therein, the only time an administration frequency is recited with a dose range in Salfeld is in Example 4, part D, section III (col. 43, lines 6-8), where a thrice a week frequency is used: "[e]ach group received three i.p. injections per week of the indicated treatments" (emphasis added). The minimal dose tested in this experiment is 1.5 mg/kg (col. 43, line 2).

As noted above, the claims as amended are directed to methods comprising the administration of a human anti-TNFα antibody, or an antigen-binding portion thereof, at a weekly low dose of 0.01-0.21 mg/kg or 0.06-0.21 mg/kg.

Therefore, even assuming for the sake of argument that Salfeld indeed teaches that the dose range and administration frequency are results effective variables (a point with which Applicants disagree), the presently claimed combination of the recited dose ranges coupled with the administration frequency clearly falls outside of the disclosure of Salfeld, which does not teach weekly administration of a low dose of a human anti-TNFα antibody, or antigen-bindng portion thereof (*i.e.*, 0.01-0.21 mg/kg or 0.06-0.21 mg/kg). As a result, optimizing the ranges in Salfeld would not lead one of ordinary skill in the art to arrive at the presently claimed methods comprising weekly low dose administration of a human anti-TNFα antibody, or antigen-binding portion thereof.

Schattenkirchner Reference (in view of Kim)

The Examiner has maintained that a further expectation of success comes from the Schattenkirchner reference itself, because the patients enrolled in that study "were not treatment naïve, i.e., and they had previously failed a mean of 3.5 DMARDs." Thus the Examiner argues that one of ordinary skill in the art "could reasonably expect to be able to titrate the dose of D2E7 for patients who are newly diagnosed and therefore have not already sustained irreversible joint damage (see Kim, page 473, Introduction), and therefore would be ***reasonably predicted to respond better to anti-TNFα treatment*** than the patients successfully treated by Schattenkirchner with 0.5 mg/kg/week D2E7." (emphasis added)

Based on the quote emphasized above, it appears that the Examiner believes that newly diagnosed RA patients respond better to treatment than patients who have had the disease longer and have failed to be treated with traditional DMARDs. Applicants note, however, that the Kim reference is directed to early diagnosis of RA. This is important, as noted by the authors, because:

> [w]ith the increased number of currently available treatment and the advent of newer targeted biologic agents, the possibility of great therapeutic benefit must be weighed against potential short- and long-term (sometimes unknown) toxicity for each patient. It appears increasingly clear that the greatest potential for limiting the disability resulting from RA lies in identifying and treat the disease in its earliest phases, before damage has been done. (Introduction, page 473, 1st column, 2nd paragraph).

Kim does not imply that newly diagnosed patients are easier to treat, but that by diagnosing patients with RA earlier, treatment may be able to stop disease progression "before damage is done". With the exception of the first sentence in the passage quoted above, Applicants note that the Kim reference is silent with regards to drugs or treatment of RA. Furthermore, nothing in the Schattenkirchner reference implies that the patients being treated are more difficult to treat than newly diagnosed patients given the same drug. Applicants respectfully request clarification of the source of the support for the Examiner's argument, *e.g.*, that newly diagnosed patients are "reasonably predicted to respond better to anti-TNFα treatment" than the patients of Schattenkirchner.

Applicants submit that this argument of the Office Action is predicated on importing one or more limitations (regarding time since diagnosis of RA or prior treatment outcomes) that are not in the claims. Furthermore, the Examiner's notion that patients who have had RA longer, or who have failed other treatments, are more difficult to treat with a human anti-TNFα antibody, or

antigen-binding portion thereof, has no support in the cited references. Thus the argument fails to show that one of ordinary skill in the art would have had a reasonable expectation of success in arriving at the presently claimed invention.

Stephens Reference

With regard to the Stephens reference, the Examiner states in the Office Action mailed August 5, 2010 that "[y]et further expectation of successfully lowering the dose of Schattenkirchner comes from the teachings of Stephens" (page 12, 7th paragraph). The Examiner proceeds by presenting several quotes from the reference on page 12, 8th paragraph to page 13, 3rd paragraph, of the Office Action:

- "Stephens describes a clinical trial of the humanized anti-TNFα antibody CDP571 where rheumatoid arthritis [patients] were administered a single dose of 0.1, 1.0 or 10.0 mg/kg CDP571 (see page 326, 2nd paragraph)."
- "Stephens further teaches patients who received placebo did not improve whereas CDP571 had a dose-dependent effect on all patients treated (see page 327, 4th paragraph)."
- "Stephens further teaches, all patients receiving CDP571 scored a reduction in pain scale by week 1 (see page 327, 4th paragraph)."
- "The quote from Stephens teaching the above two points is as follows: 'First infusion - Patients who recieved placebo did not improve. *In contrast, there was a dose-dependent effect of CDP571 treatment* with maximum patient responses after 10 mg/kg....*All patients who received CDP571 scored a reduction in pain scale by week 1*' See, ibid." (emphasis added)

The Examiner then states that "the teachings of Stephens would undoubtedly be recognized by one of ordinary skill in the art to represent at least one published attempt at using a dose of 0.1 mg/kg anti-TNFα antibody" (page 13, 5th paragraph). Thus, the Examiner alleges that one of ordinary skill in the art would have had a reasonable expectation of success in lowering the dosage of Schattenkirchner based on the teachings of Stephens. Applicants respectfully disagree.

Applicants respectfully submit that the Examiner has not responded to Applicants' arguments presented in the previous response to Office Action submitted February 2, 2011. Notably, Applicants' previous arguments make reference to the data presented in Tables 2 and 3 of Stephens. While the Examiner's arguments appear to be solely based on statements made by

Stephens in the text of the article, Applicants respectfully submit that one of ordinary skill in the art would examine the data presented in the tables in order to provide context to the conclusions drawn by Stephens, in particular for the 4th paragraph of page 327, as Stephens points one of ordinary skill in the art to these tables, in the 3rd paragraph of page 327: "[t]he results of key variables after the first and second infusions of investigational drug are summarized in Tables 2 and 3." With regard to the Examiner's previous assertion that Applicants' arguments "do not comport with the literal teachings of Stephens" (see, for example, Office Action mailed August 5, 2010, page 15, 1st paragraph), Applicants respectfully assert that the data presented in the tables are part of the literal teachings of Stephens, and that one of ordinary skill in the art would understand that the statements made by Stephens in the 4th paragraph of page 327 are based on the data of the tables referred to in the paragraph immediately preceding.

In the 4th paragraph of page 327, Stephens specifically refers to the placebo group, the 1 mg/kg group and the 10 mg/kg group, but there is no mention of the 0.1 mg/kg infusion group. As noted above, Stephens specifically points the reader to Tables 2 and 3 immediately before making the statements that are quoted by the Examiner, stating that the tables provide "the results of key variables." One of ordinary skill in the art would notice upon review of the tables that there is ***no reference to, and no data provided for***, the 0.1 mg/kg treatment group in either Tables 2 or 3. Based on this absence of reference and data in the tables, one of ordinary skill in the art would have understood that the conclusions regarding CDP571 treatment presented in the 4th paragraph of page 327, ***being based on the data of Tables 2 and 3 referred to by the authors, apply only*** to the 1 mg/kg and 10 mg/kg infusion groups, since these are the only treatment groups for which data is presented in the Tables. This conclusion would have been further supported by the lack of any specific reference to the 0.1 mg/kg group in the Results section, including the 4th paragraph of page 327. Applicants respectfully submit that the assertions made by the Examiner, *i.e.*, that the statements of the 4th paragraph of page 327 apply to the 0.1 mg/kg group, are unwarranted and unsupported by the reference itself.

With regard to the Examiner's allegation that "Stephens further teaches, all patients receiving CDP571 scored a reduction in pain scale by week 1 (see page 327, 4th paragraph)", one of ordinary skill in the art, upon review of Table 2, would have noticed that ***the placebo group also score a reduction in pain scale by week 1***. One of ordinary skill in the art would have then realized that the statement quoted by the Examiner has no implications regarding the efficacy of treatment, ***since the same effect noted by the authors was also seen in the placebo (control) group***. Thus even if the statements made by Stephens in the 4th paragraph of page 327 applied to

the 0.1 mg/kg group, which Applicants submit they do not, it would still not provide any suggestion to one of ordinary skill in the art that a dosage of 0.1 mg/kg has any efficacy in the treatment of RA.

The Examiner points to the Description of the Clinical Study section of page 326, 2nd paragraph, as referencing the 0.1 mg/kg infusion group. One of ordinary skill in the art would notice that the lack of any specific reference to the 0.1 mg/kg group in the remainder of that section or the Results section that follows. Furthermore, one of ordinary skill in the art, presented with the next specific reference to the 0.1 mg/kg group in Stephens, found in the Pharmacokinetics section that follows the Results section ("[b]ecause of the study design (placebo, 0.1, 1 or 10.0 mg/kg in the first phase and then randomization to 1 or 10 mg/kg) ..." (see page 330, 4th paragraph)), would have understood that the 0.1 mg/kg group was treated the same as the placebo group in second and subsequent phases of the study (*i.e.*, folded into either the 1 mg/kg group or the 10 mg/kg group). Given the facts above regarding the lack of data for the 0.1 mg/kg group in Tables 2 and 3, the lack of any specific reference to the 0.1 mg/kg group in Results section, and further given that the 0.1 mg/kg group was treated the same as the placebo group in the later phases of the study, one of ordinary skill in the art would have reasonably concluded that the 0.1 mg/kg dosage failed to provide any benefits to the patients receiving it.

Thus with regard to the Examiner's assertion that "the teachings of Stephens would undoubtedly be recognized by one of ordinary skill in the art to represent at least one published attempt at using a dose of 0.1 mg/kg anti-TNFα antibody", Applicants respectfully assert that one of ordinary skill in the art would interpret the teachings of Stephen to be evidence that using a dose of 0.1 mg/kg of an anti-TNFα antibody **was either an attempt that failed or inconclusive at best**.

Furthermore, Applicants note the numerous statements in the 4th paragraph of page 327 regarding the superiority of the 10 mg/kg dosage (*e.g.*, "there was a dose-depednent effect of CDP571 treatment with maximum patient responses after 10 mg/kg"; "[a]fter 10 mg/kg CDP571, the pain score was reduced by a maximum of 40% by 2 weeks (difference from placebo group statistically significant, p=0.024, adjusted), with evidence of improvement still at 8 weeks"; "[t]here was a trend to reduction in the duration of early morning stiffness after 10 mg/kg CDP571"). Given the failure of the 0.1 mg/kg dosage and the superiority of the 10 mg/kg dosage in comparison to the 1 mg/kg dosage, Applicants respectfully submit that the reference

effectively *teaches away* from reducing dosages of anti-TNFα antibodies below 1 mg/kg for the treatment of RA.

Based on the above, Applicants respectfully submit that the Stephens reference fails to provide one of ordinary skill in the art with any motivation to combine the references and lower the dosage of Schattenkircher and does not provide any reasonable expectation of success, ***given that Stephens presents no evidence or suggestion that a dosage lower than 1 mg/kg would provide a benefit*** and moreover effectively teaches away from dosages lower than 1 mg/kg, such as the dosage ranges of the instant claims, *i.e.* 0.01-0.21 mg/kg and 0.06-0.21 mg/kg.

In conclusion, Applicants submit that one of ordinary skill in the art would not arrive at the claimed weekly low doses of 0.01-0.21 mg/kg and 0.06-0.21 mg/kg based on the cited references. **Den Broeder** provides no motivation or reasonable expectation of success to attempt a dosage lower than 0.25 mg/kg, as the reference teaches that nearly 90% of patients fail treatment with doses less than 0.5 mg/kg. **Salfeld** does not make up for the deficiencies of the other references, as it suggests a wide dosage range of between 0.1-20 mg/kg, with the only relevant disclosure about frequency being three times a week, and each time at doses at least about 8-300 fold higher than the claimed range. As noted above, **Stephens** provides no data, evidence or comments indicating that the 0.1 mg/kg dose had any effect for alleviating any of the symptoms required by the claims, and by demonstrating the effectiveness of the 10 mg/kg group in comparison to the 1 mg/kg group, effectively teaches away from a lower dosage range. Furthermore, **Schattenkirchner and Kim** are not relevant since there is no teaching or suggestion in either reference that newly diagnosed patients are "reasonably predicted to respond better to anti-TNFα treatment" than other patients. Therefore, none of the cited art provides motivation or reasonable expectation of success to modify the primary reference and arrive at the claimed invention and a *prima facie* case of obviousness is not established. Reconsideration and withdrawal of the rejection of claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 as being obvious over Schattenkirchner, in view of den Broeder, Salfeld, Kim, and Stephens is respectfully requested.

Rejection of Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 Under 35 U.S.C. § 103(a)

The Examiner has maintained the rejection of claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45 and 48, and newly applied this rejection to claims 60-62, under 35 U.S.C. § 103(a) as allegedly being obvious over den Broeder in view of Salfeld, "essentially for the reasons of

record as put forth in the Office Action mailed August 5, 2010." Applicants respectfully traverse the rejection.

In the Office Action mailed August 5, 2010, the Examiner argues that it would have been obvious to further lower the dose (0.25 mg/kg per 2 weeks) in den Broeder so as to minimize cost and the risk of infection resulting from TNFα suppression, in view of the Salfeld teaching to adjust the dose and frequency as a result effective variable. Applicants respectfully disagree.

The Examiner relies on den Broder for suggesting smaller doses than 0.25 mg/kg (see, for example, the 2nd paragraph of page 19 of the Office Action mailed August 5, 2010). Applicants respectfully disagree with the Examiner's characterization of the reference. As noted by the authors in the paragraph from which the Examiner took the quotation:

> [i]n spite of the relatively small number of patients, we found marked variation in the required dose of anti-TNF-α. Required doses ranged from 4.1 to 130 mg/week. Using the titration regimen described above, the median weekly amount of anti-TNF-α given to these patients could be lowered by 67%, ***from 97.5 to 32.5 mg/week***. As no smaller *dose* ***steps*** than 0.25 mg /kg were included, one could speculate that ***even further reduction*** is possible for individual patients. (page 641, 2nd paragraph, emphasis added)

First, it is clear that the authors are referring to all of the "required doses" found in the study and to the total reduction in the "median weekly amount of anti-TNF-α given to these patients". Thus, in contrast to the Examiner's characterization of the passage, the authors are **not** speaking with "respect to the patients treated with 0.25 mg/kg/2-4 weeks". With regard to the recitation of "0.25 mg/kg", Applicants submit that den Broeder was referring to the smallest dose ***step*** used in the titration scheme, and ***not*** to the smallest dose attempted for treatment of RA. With regard to the "even further reduction" possible, Applicants submit that den Broeder is referring to further reductions in weekly dosages in terms of mg/week and ***not***, as implied by the Examiner, to further reductions in the smallest attempted dosage in terms of mg/kg. Thus the subject of the passage quoted from by the Examiner is focused on the results of the titration scheme and how the titration scheme could be further refined to determine the most optimal dosages for patients *within the dosage ranges of the titration scheme*, and not directed to further reductions in the lowest dosage attempted, as implied by the Examiner.

The Examiner also states that "den Broeder further teaches that by using the lowest possible dose of anti-TNFα antibody, one can minimize the risk associated with TNFα suppression, such as susceptibility to some infectious disease that would normally be fought off by the proinflammatory acitivity of TNFα" (see page 19, 4th paragraph). But with regard to the

"lowest possible dose", the data presented in den Broeder shows that 86% of patients do not achieve treatment with doses lower than 0.5 mg/kg. Thus while den Broeder teaches the possible advantages of generally lowering doses, the reference does not provide motivation or a reasonable expectation of success in doses lower than 0.5 mg/kg.

With regard to the Salfeld reference, as noted above, the range of Salfeld quoted by the Examiner (*i.e.*, 0.1 mg/kg to 20 mg/kg) makes no reference to dosing frequency, and furthermore Salfeld makes no references to the claimed low doses (*i.e.*, 0.10-0.21 mg/kg; 0.06-0.21 mg/kg; 0.06-0.16 mg/kg; 0.06-0.11 mg/kg; and 0.09-0.11 mg/kg). Applicants also reiterate (which the Examiner does not dispute) that the only time an administration frequency is recited with a dose range in Salfeld is in Example 4, part D, section III (col. 43, lines 6-8), where a thrice a week frequency is used: "[e]ach group received three i.p. injections per week of the indicated treatments" (emphasis added). The minimal dose tested in this experiment is 1.5 mg/kg (col. 43, line 2). By teaching 1.5 mg/kg three times a week as a minimal dose, the Salfeld reference provides no motivation or reasonable expectation of success in lowering the doses of den Broeder, given less frequently.

Based on the lack of suggestion or motivation in either reference, alone or combined, and the lack of a reasonable expectation of success in reducing the lowest dosage of den Broeder, Applicants submit that a *prima facie* case of obviousness is not established. Reconsideration and withdrawal of the obviousness rejection of claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 is respectfully requested.

Rejection of Claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62, under 35 U.S.C. § 103(a) as allegedly being obvious over Pluenneke (U.S. Patent Application Publication No. 2001-0021380 A1). The Examiner asserts that "Pluenneke teaches a method of treating RA comprising administering the D2E7 anti-TNFα antibody at a dose of 0.1-20 mg/kg on a weekly basis" and that:

> [g]iven that the range of Pluenneke 0.1 - 20 mg/kg overlaps the claimed range - "about" 0.06- 0.21 mg/kg - and further given the uncertainty about the meaning of "about" put forth above, it is prima facie obvious that one of ordinary skill in the art following the teachings of Pluenneke would arrive at the claimed method of treatment.

> This because, as is made clear from the teachings of Pluenneke, e.g., at paragraphs 22-29, the determination of the dosage regimen of a known drug is well within the purview of one of ordinary skill in the art at the time the invention was made and it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal intervals of treatment because optimal intervals is an art-recognized result-effective variable which would have been routinely determined and optimized in the pharmaceutical art. (4th and 5th paragraphs, page 11 of Office Action)

The Examiner also states that "it should be noted that in the case where claimed ranges 'overlap or lie inside ranges disclosed by the prior art' a prima facie case of obviousness exists." Thus the Examiner takes the position that, based on the disclosure of Pluenneke and the term "about" as used in the claims with regard to dosage ranges, one of ordinary skill in the art could have arrived at the present invention through routine optimization. Applicants respectfully traverse the rejection.

As noted in MPEP § 2144.05 part I, "if the reference's disclosed range is so broad as to encompass a very large number of possible distinct compositions, this might present a situation analogous to the obviousness of a species when the prior art broadly discloses a genus." Furthermore, "Applicant can rebut a presumption of obviousness based on a claimed invention that falls within a prior art range by showing '(1) [t]hat the prior art taught away from the claimed invention...or (2) that there are new and unexpected results relative to the prior art.'" (See MPEP §2144.05 part III).

As noted above, the claims have been amended to delete the term "about". The claims are directed to ***specific dosage ranges***, *e.g.*, 0.10-0.21 mg/kg and 0.06-0.21 mg/kg.

In addition, Applicants note that the paragraphs of Pluenneke cited by the Examiner (paragraphs [0022]-[0029]) disclose characteristics of a TNFα-binding soluble receptor, "preferable TNFR:Fc" (see paragraph [0022]), whose dosage ranges are provided in mg/m^2, *i.e.*, in units of drug mass per body surface area. Thus paragraphs [0022]-[0029] of Pluenneke disclose an agent that is not an antibody, let alone a fully human antibody against TNFα, and that requires a different method of measurement of patient-specific dosage ranges. The only disclosure in Pluenneke that relates to dosage ranges for antibodies against TNFα is found in the first two sentences of paragraph [0032]:

> If an antibody against TNFα is used as the TNFα inhibitor, a preferred dose range is 0.1 to 20 mg/kg, and ***more preferably*** is 1-10 mg/kg. Another preferred dose range for anti-TNFα antibody is 0.75 to 7.5 mg/kg of body weight.

Applicants respectfully point out that the more preferred dosage range does not overlap the dosage ranges of the present claims. Given that two of the three dosage ranges provided by Pluenneke do not overlap with the claimed dosage ranges and that the ***more preferred*** dosage range of Pluenneke is nearly 5 fold to nearly 50 fold greater than the maximum dosage of the claimed dosage ranges, Applicants submit that Pluenneke ***teaches away*** from the present invention, by indicating that dosages nearly 5 to 50 fold higher than the highest dosage of the present invention are ***more preferred*** than any lower dosage. Thus one of ordinary skill in the art would not be motivated to attempt the claimed dosage ranges, nor would one of ordinary skill in the art have any expectation of success in doing so.

With regard to the one dosage range disclosed by Pluenneke that does overlap with the presently claimed dosage ranges (*i.e.*, 0.1 to 20 mg/kg), the upper limit of that dosage range is a nearly 100 fold greater dosage that the maximum dosage of the present claims. The Pluenneke range covers 19.9 mg/kg of dosage units, whereas the broadest of the claimed dosage ranges (0.6-0.21 mg/kg) covers 0.11 mg/kg. Applicants respectfully submit that as Pluenneke's disclosed overlapping range is so broad as to encompass a very large number of possible dosage ranges on the scale of those of the present claims and thus the claimed dosage ranges are not obvious in view of the much broader Pluenneke overlapping range, per MPEP § 2144.05 part I.

The disclosure of Pluenneke does not provide any motivation or expectation of success to one of ordinary skill in the art to modify the teachings of the reference, and actually teaches away from the presently claims ranges. Furthermore, as the presently claimed ranges are 180 fold smaller than the only overlapping range of Pluenneke, the presently claim ranges can at best be considered "species" of the "genus" provided by the overlapping range of Pluenneke, per MPEP § 2144.05 part I, and thus are not rendered obvious by the much broader Pluenneke range. In view of the above, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 15-17, 21, 22, 24, 31, 34, 35, 42, 43, 45, 48 and 60-62, under 35 U.S.C. § 103(a) as obvious over Pluenneke.

CONCLUSION

Applicants submit that the pending claims are in condition for allowance. If a telephone conversation with Applicant's Attorney would expedite the prosecution of the above-identified application, the Examiner is urged to call the undersigned at (617) 449-6500.

The Commissioner is hereby authorized to charge any fees associated with the filing of this communication to our Deposit Account No. 50-4876, from which the undersigned is authorized to draw under Order No. 117813-99302.

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Respectfully submitted,

Electronic signature for / MLZ /
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